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HERBERT H JERVIS
SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-UW2220
P O BOX 1539
KING OF PRUSSIA PA 19406-0939

DATE MAILED: 05/20/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on 1/29/96 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. 1 page
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-7, 10-18 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 8 and 9 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-7, 10-18 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☒ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☒ been filed in parent application, serial no. 08/356,372; filed on 2/17/95.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. The examiner acknowledges the cancellation of claims 8 and 9 and the addition of claims 13-18.

17. Claims pending are claims 1-7, 10-18.

18. The objection to the specification because of informalities is withdrawn in view of applicant's amendments.

19. The rejection of claims 1-12 under 35 U.S.C. §112 second paragraph as failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicant's amendments to the claims and cancellation of claims 8 and 9.

20. The examiner acknowledges the substitute specification which is in compliance with 37 CFR 1.52(b) and (c).

21. The examiner acknowledges the preliminary amendment in which claims 1, 3-12 were amended to conform to U.S. practice. The office action mailed 7/24/95 was in fact directed to those claims as amended in the preliminary amendment as all depending from claim 1.

Applicant's arguments filed 1/29/96 have been fully considered but they are not deemed to be persuasive.

22. The provisional double patenting rejection of claims 1-7, 10-12 and newly presented claims 13-18 under 35 U.S.C. §101 is maintained for reasons set forth in paper no. 4,

paragraph 18 of the previous office action. The examiner notes applicant's statement concerning cancelling claims upon notification of allowable subject matter.

23. The objection to the specification and rejection of claim 6 under 35 U.S.C. §112 first paragraph as the disclosure is enabling only for claims limited to an antigenic composition of glycoprotein D and CS protein from malaria in combination with the adjuvants 3D-MPL and QS-21, a method of making the antigenic composition and a method of stimulating cytolytic T cells and gamma interferon production is maintained essentially for reasons set forth in paper no. 4, paragraph 19 of the previous office action.

The rejection was on the grounds that the claims are broadly drawn to a vaccine composition comprising antigen derived from all viral, bacterial or parasitic infections as well as to human immunodeficiency virus and feline leukemia virus. The specification lacks enablement for vaccine compositions which would be effective against all of the claimed species of pathogenic infections, particularly against HIV, prophylactically or therapeutically. The specification provides no probative evidence to support a vaccine which would protect humans against AIDS. The obstacles to vaccine development and therapeutic approaches with regard to retroviruses associated with AIDS in humans are well documented in the literature. These obstacles include: 1) the extensive genomic diversity associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein, 2) the fact that the modes of viral transmission include virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert form, as well as via free virus transmission, 3) existence of a latent form of the virus, 4) the ability of the retrovirus to "hide" in the central nervous system where blood cells and neutralizing agents carried by the blood cannot reach the retrovirus, due to the blood-brain barrier and 5) the complexity and variation of the elaboration of the disease. The existence of these obstacles establish that the contemporary knowledge in the art would prevent one of ordinary

skill in the art from accepting any vaccine or any immunization treatment or any therapeutic regimen on its face. In order to enable claims to drugs, antigenic compositions and their uses, either in vivo or in vitro data, or a combination of these can be used. However, the data must be such as to convince one of ordinary skill in the art that the proposed claims are sufficiently enabled. See In re Irons, 340 F.2d 924, 144 USPQ 351 (CCPA 1965), Ex parte Krepelka, 231 USPQ 746 (PTO Bd. Pat. App. & Inter. 1986) and Ex parte Chwang, 231 USPQ 751 (PTO Bd. Pat. App. & Inter. 1986). By definition vaccines must not only induce an immune response, but must be immunogenic to the extent that upon subsequent challenge with the live virus, development of the disease is prevented, or better yet infectivity does not occur.

The development of immune responses important in protection against HIV infection has not been established. Generally it is thought that humoral immunity as well as cell mediated immunity are important in recovery from viral infections. The generation of neutralizing antibody responses against HIV have not been well correlation with slowing or preventing HIV infection. Cohen et al have reported that neutralizing antibodies have been unable to neutralize what is known as "primary field isolates" of HIV, which isolates are more closely related to that which would infect the general population (page 980). Similarly the development of cytolytic responses has not been correlated with the slowing of progression to HIV disease. Butini et al, in comparing CTL activity in lymphoid tissue and peripheral blood found HIV-specific CTL activity in a patient with rapidly progressive disease, while in another patient showing no progression of immunodeficiency, no CTL activity (abstract J306). Thus it is not clear what factors or parameters constitute immunity to HIV disease. Additionally, the claims are drawn to vaccine compositions against feline leukemia virus. This virus appears to be a virus specific to the feline animal species while the others appear to cause infections in humans. The specification lacks enablement for the claimed adjuvant compositions and the feline leukemia virus and enablement to show that the claimed adjuvants are effective in the feline animal species. In view of all of the above and in view of the lack of guidance provided by the specification with respect to the enablement of the broad claims, it is determined that the specification is not commensurate in scope with the claimed subject matter.

Applicant urges that with respect to HIV, clinical trials are proceeding but results are unavailable, the rejection appears to be based upon utility, the specification contains sufficient

data to support the broad scope of the claimed subject matter. Applicant additionally urges that a Declaration under 1.132 will be filed providing additional data if needed and cites In re Vaeck, In re Gardner, and Atlas Powder Co. v. E.I. Dupont de Nemours in support.

It is the examiner's position that claim 6 is broadly drawn to several different species of organisms which include the human immunodeficiency virus. The specification lacks enablement for a vaccine composition, particularly against HIV infection. The obstacles to the development of vaccines and treatment therapies against HIV have already been outlined and discussed in the previous office action. Applicant has stated that antigens form opposite ends of the spectrum were chosen and tested. However, it is not apparent from the specification, that one would reasonably expect particulate or soluble antigens from, for example, HIV to function similarly, particularly in view of the lack of correlation between in vitro results and in vivo efficacy associated with HIV. The immune correlates of HIV infection have yet to be determined and the instant specification lacks sufficient guidance and teaching to show that one would reasonably expect particulate and insoluble HIV antigens to function similarly to CS and glycoprotein D antigens, as disclosed in the instant specification. In view of all of the

above, the specification is not commensurate in scope with the claimed subject matter.

24. The rejection of claims 1, 2, 5, 6, 10, 12 and newly presented claims 13 and 14 under 35 U.S.C. §103 as being unpatentable over Long et al, 1984 in view of Kensil et al, U.S. Pat. No. 5,057,540 and further in view of Schneerson et al, 1991 is maintained essentially for reasons set forth in paper no. 4, paragraph 22 of the previous office action. It should be noted that this is a new grounds of rejection with respect to newly presented claims 13 and 14.

The rejection was on the grounds that Long et al describe the protection of mice from lethal challenge with herpes virus, after administration of herpes virus glycoprotein D in adjuvant (abstract and table 1). The administration of glycoprotein D conferred protection against lethal challenge with both homologous and heterologous virus types (page 763, first column). Glycoprotein D generated high levels of neutralizing antibody titres (pages 761-763 and table 1). Long et al differ from the claimed invention in not specifically describing the use of QS-21 or 3D-MPL in the antigenic composition.

Kensil et al teach compositions of saponins and antigens and the effectiveness of saponins (from *Quillaja saponaria* bark) such as QA-21, QA-17 and QA-18 as adjuvants in antigenic compositions (abstract, figures 12-15 and columns 20-23). Saponins are natural products and may be used as immune adjuvants (col. 3, lines 8-46). The effective ratios of adjuvant to antigen suggested are "3.0 or less or preferably 1.0 or less" (col. 7, lines 10-13). The saponins, particularly QA-21 (col. 5, lines 30-35) which appears to be similar or an obvious or analogous variant of the claimed QS-21, may be administered individually or admixed with other substantially pure adjuvants to "achieve the enhancement of the immune response to an antigen" (col. 7, lines 14-20). While Kensil, et al suggest the use of QA-21 in admixture with other adjuvants, Kensil et al do not specifically describe 3-De-O-acylated monophosphoryl lipid A (3D-MPL) as an adjuvant. However, Schneerson et al describe the enhancement of serum antibody responses in mice to polysaccharide antigens in combination with MPL as adjuvant (abstract, page 213,

tables 1-6). Antigen in combination with MPL, which MPL appears to be similar or an obvious or analogous variant of the claimed 3D-MPL, when administered, generated higher specific serum antibody responses. Schneerson et al also describe compositions of MPL and other adjuvants with antigen at ratios of 1:1 (page 213, tables 2-5). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include QS-21 and 3D-MPL in an antigenic composition with antigen as suggested by Kensil et al and Schneerson et al. It would have been expected, barring evidence to the contrary, that the addition of QS-21 and 3D-MPL to glycoprotein D subunit vaccine of herpes simplex virus of Long, et al, would be effective in enhancing the neutralizing antibody response to glycoprotein D, resulting in protection against infection with herpes virus types 1 and 2. The use of a particular ratio of QS-21 to 3D-MPL is well within the level of skill in the art, would be a matter of empirical determination and design choice.

Applicant urges that Long et al disclose gD of herpes simplex in combination with Freund's complete adjuvant, only antibody responses are disclosed, no CTL responses are disclosed, there is no suggestion to use an adjuvant other than Freund's and the last sentence of Long states that it remains to be seen if the test vaccine is protective against the establishment of latency of recurrent infection.

It is the examiner's position that the claims do not recite humoral or CTL responses (i.e. claims 1, 2, 5, 6, 10, 12, 13, 14). The claims are drawn to a vaccine composition comprising antigen and the QS21 and 3D-MPL adjuvants. The claims are also not drawn to a method of inhibiting the establishment of latency of recurrent herpes simplex virus infection. Long et la disclose that immunization with adjuvanted glycoprotein D from Herpes Simplex Virus types 1 and 2 can protect against lethal

challenge with Herpes virus. It is very well known in the art that Freund's complete adjuvant is not suitable for human use. Thus the ordinarily skilled artisan would be motivated to use an adjuvant other than Freund's complete adjuvant, if contemplating human use. However, it should be noted that the claims are not limited to the use of the compositions in humans.

Applicant urges that Kensil et al do not suggest the use of QS-21 in conjunction with 3D-MPL. Applicant urges that Kensil et al disclose the use of mixtures of saponin and/or non-saponin adjuvants but does not suggest that there is synergism with the addition of another adjuvant. Applicant additionally adds that Kensil et al only disclosed one working example to support their broadly claimed subject matter.

It should be noted that neither applicant nor the examiner is knowledgeable of the prosecution history of the application which resulted in U.S. Pat. No. 5,057,540 or what additional evidence was presented or what additional data were presented. It is the examiner's position that applicant appears to argue the references individually without clearly addressing the combination of references. Kensil et al suggest the following:

a) the use of QS-21 adjuvant to enhance immune responses

b) mixtures of the saponin adjuvant which enhanced antibody responses two orders of magnitude greater when the antigen was administered without adjuvant (column 4, lines 20-28)

c) the effectiveness of the saponin adjuvants at lower doses (column 5, lines 28-34)

d) the administration of saponin together with non-saponin adjuvants from a variety of other adjuvant sources (column 7, lines 14-40) and

e) a method of administering a composition comprising antigen and a mixture of saponins (columns 20-22).

Applicant urges that the tertiary reference relates to MPL and not 3D-MPL and only in combination with TDM, there is no suggestion of other adjuvants which can be used and the combination of references is improper citing in support, for example, In re Imperato, In re Nomiya, In re Fine and In re Ochiai. It appears that the cited case law is not particularly relevant to the instant invention. Contrary to the facts presented in for example, In re Nomiya or In re Fine, the cited combination of teachings in the instant application expressly suggests a mixture of antigen and adjuvants and a suggestion of an enhanced immune response which would be two orders of magnitude greater than a response absent adjuvants. Additionally, one of ordinary skill in the art realizing that Freund's Complete Adjuvant is not suitable for human use would be motivated to use an adjuvant other than Freund's Complete Adjuvant particularly if contemplating human use. These facts appear to be contrary to those in the cited case law.

It is the examiner's position that again applicant appears to argue the references individually as if each was anticipatory under 35 U.S.C. §102. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which make up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Moreover, specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America (DC SNY) 202 USPQ 22; and In re Burckel (CCPA 201 USPQ 67). It should be noted that it was stated that the adjuvant described by Schneerson et al appears to be an obvious or analogous variant of the claimed adjuvant. There is nothing on record to show that the MPL of the prior art reference would not function similarly to the claimed 3D-MPL adjuvant. Indeed, applicant has submitted a reference (Myers, U.S. Pat. No. 4,912,094) which states that all of the uses disclosed in the literature for MPL can be

entertained with respect to d3-MPL (col. 9, lines 62-68). Thus it would appear that the criticality of using 3D-MPL as opposed to MPL has not been established in the instant specification. The combination of teachings of the prior art has suggested the use of antigen in combination with a mixture of adjuvants (saponin and/or non-saponin), and the art suggests that lower doses of saponin may be used to enhance the immune response at least two orders of magnitude higher. Schneerson et al suggest the use of MPL, which appears to be an obvious variant of the claimed 3D-MPL, in combination with TDM to enhance antibody response to antigen. It would follow then, that the combination of QS-21 + MPL + antigen would at least enhance an immune response two orders of magnitude higher, absent evidence to the contrary. It should be noted that the claims are drawn to a vaccine or pharmaceutical composition employing the open ended terminology "comprising". Applicant's use of the open-ended term "comprising" in the claims fails to exclude unrecited steps and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. See In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948).

25. The rejection of claims 1, 3, 4, and newly presented claims 15-18 under 35 U.S.C. §103 as being obvious over Schofield et al or Weiss et al in view of Kensil et al and further in view

of Schneerson et al is maintained essentially for reasons set forth in paper no. 4, paragraph 23 of the previous office action. It should be noted that this is a new grounds of rejection with respect to newly presented claims 15-18.

The rejection was on the grounds that Schofield et al describe the immunization of rats with irradiated *Plasmodium berghei* sporozoites. The immunization with irradiated sporozoites generated humoral immunity as well as cell mediated immunity with the development of gamma interferon producing (γIFN) cytotoxic T cells, indicating the involvement of cytotoxic cells and γIFN in the development of immunity to malaria sporozoites (page 668). Likewise, Weiss et al describe immunization of mice with live sporozoites and the development of T cell-mediated immunity (abstract, page 573 and tables 1-3). Schofield, et al and Weiss et al differ from the claimed invention in not specifically describing antigenic compositions comprising QS-21 and 3D-MPL. However, the teachings of Kensil et al and Schneerson et al have already been described above. Thus it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include 3D-MPL and QS-21 in an antigenic composition of live or irradiated sporozoites. It would have been expected, barring evidence to the contrary, that the antigenic composition would generate enhanced cytolytic T cell responses and γIFN production which would result in enhanced immunity to malaria sporozoites.

Applicant urges that Weiss states that CD8+ T cells are required for protection, immunization with irradiated sporozoites is impractical, Schofield et al as well as Weiss et al do not offer solutions to the problem of the need for γ-interferon production and T cell mediated immunity and that neither of the references in combination with the secondary or tertiary references teaches or suggests the claimed invention.

It is the examiner's position that Weiss et al establish the importance of T cell mediated immunity to parasitic infections such as malaria. the antigen employed was irradiated

sporozoites. It is stated that humans have been successfully immunized with irradiated sporozoites. It is also stated that the use of attenuated parasites is impractical. However, it should be noted that the claims are not limited to human malarial organisms or the use of the vaccine composition in humans. Schofield et al additionally establish the need for γ-interferon, CD8+ T cells and antibodies in immunity to the antigen, malaria sporozoites. The combination therefore of irradiated malaria sporozoite antigen as disclosed by Weiss or Schofield with QS-21 and MPL as disclosed by Kensil and Schneerson, respectively, would indeed have been obvious as has already been described above. It would have been expected, barring evidence to the contrary, that immune responses would have been generated with the addition of the mixture of adjuvants which would have resulted in at least two orders of magnitude higher than immune responses in the absence of adjuvants.

26. The rejection of claims 1, 7 and 11 under 35 U.S.C. §103 as being unpatentable over Cantrell, U.S. Pat. No. 4,877,611 in view of Kensil et al , U.S. Pat. No. 5,057,540 is maintained essentially for reasons set forth in paper no. 4, paragraph 24 of the previous office action.

The rejection was on the grounds that Cantrell describes vaccines comprising adjuvants, such as MPL, together with tumor antigens. The MPL appears to be similar or an obvious or analogous variant of the claimed 3D-MPL (abstract and cols. 3-6). It is stated that the vaccines are effective for the treatment and prevention of cancerous tumors (col. 2, lines 41-60) and can

be used to provide a protective and lasting tumor immunity (abstract, col. 10-15). It is suggested that other adjuvants can also be employed with the immunogenic compositions (col. 5, lines 34-42). Cantrell differs from the claimed invention in not specifically describing the use of QS-21 in the anti-tumor composition. However, the teachings of Kensil et al, have already been described above. Thus it would have been *prima facie* obvious to one or ordinary skill in the art at the time the invention was made to include QS-21 and MPL in an anti-tumor antigenic composition. It would have been expected, barring evidence to the contrary, that the amount of anti-tumor composition administered would be safe and effective and would enhance tumor immunity which would be protective and long lasting.

Applicant urges that Cantrell does not teach 3D-MPL, the similarity of 3D-MPL to MPL is not relevant and cites In re Ochiai in support, the reference only teaches MPL in combination with a bacterial immunostimulant and there is no suggestion to combine it with a willow bark extract.

It is the examiner's position that as has already been pointed, that applicant appears to argue the references individually, as if each were presented in support of a rejection under 35 U.S.C. §102. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which make up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Moreover, specific statements in

the references themselves which would spell out the claimed invention are not necessary to show obviousness since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America (DC SNY) 202 USPQ 22; and In re Burckel (CCPA 201 USPQ 67). Cantrell describes vaccine compositions comprising adjuvants such as MPL, which appears to be an obvious or analogous variant of the claimed 3D-MPL, together with tumor antigens. It is stated that the vaccines are effective for the treatment and prevention of cancerous tumors. There is nothing on record to show that the MPL adjuvant of Cantrell would not function similarly to the claimed 3D-MPL adjuvant. Additionally, Cantrell suggests that other adjuvants can also be employed with the immunogenic compositions. Thus it would appear that the combination of tumor antigen + MPL as suggested by Cantrell with the QS-21 of Kensil would indeed enhance the immune response and it would have been expected, barring evidence to the contrary, that the immune response would be enhanced at least two orders of magnitude higher than the composition without adjuvant.

27. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION

IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

28. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Lynette F. Smith, Art Unit 1813 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1813 FAX telephone number is (703)-305-7939. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynette F. Smith whose telephone number is (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Should the examiner be unavailable, Supervisory Patent Examiner Christine M. Nucker, may be reached at (703) 308-4028.

L. F. Smith

LYNETTE F. SMITH
PATENT EXAMINER
GROUP 1800

Smith/lfs LFS
May 15, 1996